REMARKS

Claims 17, 20, 21, 23, and 25-30 were subject to various rejections asserted in the Office Action mailed on April 15, 2008. Claims 18, 19, 22, 24 and 31 were previously cancelled. Applicants have amended claims 17, 20, 21, 23, and 25-28, and have cancelled claim 29. No new matter has been added by these amendments. In view of the amendments to the claims and remarks below, Applicants respectfully request reconsideration and withdrawal of the asserted rejections.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 28-31 have also been rejected under 35 U.S.C § 112, first paragraph, because the Office Action contends that the Specification does not enable one of ordinary skill in the art to practice a method of prophylactically treating a mammal.[1] "Prophylactically" has been deleted from claim 28. Accordingly, withdrawal of this rejection is respectfully requested.

REJECTION UNDER 35 U.S.C. § 103

On page 7, the Office Action states that "claims 18-21 are rejected under 35 U.S.C. § 103 as unpatentable over Place (US Patent 6,117,446) in view of Yamazaki (Archive of Biochemistry and Biophysics, 1997)." During a telephone interview with the Examiner on August 4, 2008, the Examiner stated that the rejection should have been asserted against claims 17, 20, 21, 23, and 25-30, and that the Office Action mailed on April 15, 2008 provides that basis to support the rejection of claims 17, 23 and 25-30. Applicants respectfully traverse this rejection for the reasons discussed below. (This rejection is moot as to claim 29 since it has been cancelled).

The Claimed Invention

Claim 17, as amended, is directed to a pharmaceutical oral dosage unit containing at least 10 μg of a steroid selected from the group consisting of 15-hydroxytestosterones,

[1] Office Action at page 2.

precursors thereof, mixtures thereof and precursors thereof said mixtures; and a pharmaceutically acceptable excipient. The oral dosage unit is selected from the group consisting of a tablet, a capsule and a chachet.

The Cited References

The Office Action contends that Place teaches a buccal drug delivery system comprising an androgenic agent, a progestin, an estrogen and a bioerodible polymeric carrier.[2] The Office Action also acknowledges that Place does not mention 15-hydroxytestosterones.[3]

The Office Action contends that Yamazaki overcomes this deficiency.[4] Yamazaki is directed to a study to elucidate how testosterone is metabolized by the liver.[5] It identifies 15-hydroxytestosterone as a metabolite of testosterone.[6] It does not state that 15-hydroxytestosterone is pharmacologically active. In fact, it does not test whether 15-hydroxytestosterone has any biological activity whatsoever.

Point I. There is no reasonable expectation within the art that all naturally occurring steroids are pharmacologically active.

The rejection is premised on the assumption that all naturally occurring steroids are believed to be pharmacologically active.[7] However, as the attached references evidence, hydroxylation of testosterone is known as a means of inactivating testosterone.[8] Harada *et al.* state that "[h]ydroxylation of steroid hormones and subsequent conjugation of hydroxylated steroids are also interesting biological functions of liver microsomes, pathways by which steroid hormones are believed to be metabolized to ***inactive*** forms."[9] Likewise, Gustafsson *et al.* state that "[i]t is speculated that the physiological role of the highly sex-specific 15β-hydroxylase

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[2] Office Action at page 7.
[3] Office Action at page 7.
[4] Office Action at page 7.
[5] Yamazaki at page 167.
[6] Yamazaki at page 167.
[7] See Office Action at page 7.
[8] Harada *et al.*, "Mouse liver testosterone 15α-Hydroxylase (Cytochrome P-450$_{15\alpha}$)," J of Biol. Chem., (Jan. 26, 1984) 259(2): 1265-1271.; Gustafsson *et al.*, "Regulation and properties of a sex-specific hydroxylase system in female rat liver microsomes active on steroid sulfates," J. of Biol. Chem., (Mar. 25, 1974) 249(6): 1940-1945.
[9] Emphasis added, Harada *et al.* at 1269.

system is to ascertain efficient hepatic ***deactivation*** of potential androgenic compounds in female rats."[10]

When making a rejection under 35 U.S.C. § 103, the examiner has the burden of establishing a *prima facie* case of obviousness. *In re Fritch*, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992). As part of a *prima facie* case, an examiner must establish some reason to combine the references. *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 131 (2007); *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-1357 (Fed. Cir. 2007). The *KSR* Court acknowledged the importance of identifying a reason that would have prompted a person of ordinary skill in the art to combine the elements in the way the claimed invention does. *KSR Int'l*, 127 S.Ct. at 1731; *Takeda Chemical*, 492 F.3d at 1356-1357. Repeatedly throughout the *KSR* decision, the Court discussed the importance that the result obtained by a particular combination was predictable to one of ordinary skill in the art. *KSR Int'l*, 127 S.Ct. at 1731 and 1739-1742.

A combination of known elements will not yield predictable results if the references teach away from the claimed invention. *Takeda Chemical*, 492 F.3d at 1359; *Ortho-McNeil Pharmaceutical, Inc. v. Mylan*, 520 F.3d 1358, 1364 (Fed. Cir. 2008); and *Ex parte Ikeda*, App. No. 08/352,079, Appeal 2008-0492, Slip Op. at 7 (BPAI Mar. 26, 2008). For example, in *Takeda Chemical*, the post-*KSR* Federal Circuit noted that the recited compound, which was a modified version of compound b, was not recognized at the pertinent time as a suitable candidate for treatment of Type II diabetes. 492 F.3d at 1359. *Takeda Chemical* involved United States Patent No. 4,687,777, which was directed to a compound for the treatment of Type II diabetes. *Id.* at 1352-1354. The defendant argued that the patent was obvious in view of a reference that disclosed compound b, because the claimed compound could be synthesized from compound b by routine means. *Id.* at 1357. However, the Federal Circuit affirmed that the patent was not obvious because the prior art taught away from choosing compound b as a starting point. *Id.* at 1359-1361. Compound b was known to have unwanted side effects, and there was nothing in the prior art to suggest that homologation would decrease the unwanted side effects. *Id.* at 1359-1360.

[10] Emphasis added, Gustafsson *et al.* at 1940.

In a more recent case, the Board reversed an examiner's rejection for failing to provide the requisite reason to combine the references. *Ikeda*, App No. 08/352,079 at 7. The *Ikeda* application was directed to a method of removing hydrocarbons from exhaust gases. *Id.* at 2. In pertinent part, the claims recited an absorption catalyst B located downstream of a catalyst A in the direction of the exhaust gas. The claims were rejected as unpatentable under 35 U.S.C. § 103 in view of Swaroop, Abe and Patil. *Id.* at 3. Swaroop taught positioning the absorption catalyst B upstream of catalyst A. *Id.* at 5. To remedy the deficiency in the art, the examiner cited "Patil and Abe as evidence of the 'coventionality of positioning the adsorbent catalyst 1 either upstream or downstream of a [three-way] catalyst 3' and thus conclude[d] that it would have been obvious to one of ordinary skill in this art to select an appropriate location for the adsorbent catalyst 16 in the apparatus of Swaroop …." *Id.* at 5-6. The Board held that

> The Examiner has failed to provide any cogent reason or technical discussion to support the conclusion that one of ordinary skill in this art would have employed the relative positions of the catalysts in Abe and Patil without the use of the other teachings of these references, namely an auxiliary heater and bypass lines with valving. Second, the Examiner has not explained why one of ordinary skill in this art would have used the teachings of Patil, requiring bypass lines and valving, when Swaroop specifically ***teaches away*** from the use of valving and bypass lines [*citation omitted*]. Third, the Examiner has not supplied convincing reasoning or technical discussion to support the proposed switch in relative position of the catalysts when Swaroop specifically teaches that the exhaust gas is "modified" by the adsorbent catalyst and this modified form of the exhaust gas is *then* sent to the main or three-way catalyst to undergo conversion to innocuous products [*citation omitted*]. … Fourth, the Examiner has not explained why one of ordinary skill in this art would have ***proceeded contrary to the teachings of Patil***, namely the teachings that "it is not possible merely to place zeolite 'in-line' in the exhaust system with the [main] catalyst has reached an effective temperature and unconverted hydrocarbons would still be discharged to the atmosphere" [*citation omitted*].

Ikeda, App. No. 08/352,079 at 7 (emphasis added).

Thus, in order to establish a *prima facie* case of obviousness, there must have been some reason why one would reasonably expect 15-hydroxytestosterone to be pharmacologically active. While Yamazaki teaches that 15-hydroxytestosterone is a naturally occurring metabolite of testosterone,[11] it does not suggest that this or any other naturally

[11] Yamazaki at page 167.

occurring metabolity of testosterone metabolite is pharmacologically active. In fact, as evidenced by the attached references, prior to the disclosure of this invention, one of ordinary skill in the art believed that 15-hydroxytestosterone would not be pharmacologically active – that it was "inactive" or "deactived".[12]

Point II. There is no reasonable expectation within the art that all naturally occurring steroids are pharmacologically active when orally administered.

Additionally, there was no reasonable expectation that all naturally occurring steroids are pharmacologically active when orally administered. The specification states that only a few androgens, e.g. dehydroepiandrosterone (DHEA) and 17alpha-alkylated derivative of testosterone, are suitable for oral administration.[13] For the reasons stated in *KSR Int'l*, *Takeda Chemical* and *Ikeda*, the Office Action must provide some reason why one would consider 15-hydroxytestosterones to be pharmacologically active when orally administered.

The Office Action has not provided such a reason because it contends that "oral" should not be given patentable weight because it purportedly is directed to an intended use.[14] Applicants respectfully disagree.

When a claim preamble is read in context of the entire claim and all the limitations of the claim, and is necessary to give life, meaning and vitality to the claim, the preamble should be construed as if in the body of the claim. "During examination, statements in the preamble reciting the purpose or intended use of the claimed invention must be evaluated to determine whether the recited purpose or intended use results in a structural difference (or, in the case of process claims, manipulative difference) between the claimed invention and the prior art. If so, the recitation serves to limit the claim."[15]

In this case, the preamble gives life, meaning and vitality to the claim. It provides a structural difference in the claimed invention because an oral dosage unit has a different structure than an intravenous dosage unit. This structural difference relates to the recitation that

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[12] See Harada *et al.* at 1269; also see Gustafsson *et al.* at 1940.
[13] Specification at page 2, lines 7-8.
[14] Office Action at page 3.
[15] MPEP § 2111.02.

the oral dosage unit is selected from the group consisting of a tablet, a capsule and a chachet. Moreover, as the specification establishes, one of ordinary skill in the art would not have reasonably expected 15-hydroxytestosterones to be pharmacologically active when orally administered. Thus, "oral" serves to further define the invention over the prior art.

For these reasons, Applicants respectfully request that the recitation of "oral dosage unit" be duly considered. Since the cited reference does not provide a reasonable expectation for 15-hydroxytestosterones to be pharmacologically active when orally administered, the recited invention is patentable under Section 103.

Point III. It was unexpected to discover that 15-hydroxytestosterone is pharmacologically active.

Furthermore, the recited invention is patentable over the cited references because it was unexpected to discover that 15-hydroxytestosterone is pharmacologically active. To establish unexpected results, the Applicant must

> establish (1) that there actually is a difference between the results obtained through the claimed invention and those of the prior art, *In re Klosak*, 455 F.2d 1077, 59 CCPA 862 (1972); and (2) that the difference actually obtained would not have been expected by one skilled in the art at the time of invention, *Id.*; *In re D-Ancicco*, 439 F.2d 1244, 58 CCPA 1057 1057 (1971).

In re Freeman, 474 F.2d 1318, 1324 (CCPA 1973). Without evidence to the contrary, an applicant need only provide substantially improved results and state that the results were unexpected. *Soni*, 54 F.3d at 750; *In re Lee*, App No. 10/091,061, 2007 WL 176690 at *3 (BPAI June 19, 2007).

In *Soni*, the examiner rejected certain claims as obvious in view of a combination of references. The applicant directed the examiner to the data in the specification, and argued that the increase in tensile strength and the increase in peel strength rebutted the rejections. *Soni*, 54 F.3d at 747. On appeal to the Federal Circuit, it was argued that the Board

> could have taken judicial notice of the fact that higher molecular weight polymers would have been expected to tolerate higher filler loadings without degradation in properties and that it could have taken notice of the fact that it is the polymer *per se* that primarily determines the mechanical properties of a filled polymer composition.

Id. at 750. However, the Federal Circuit found this argument fatally flawed because the Board failed to support its position with facts or evidence. *Id.* at 750; *see also Lee*, 2007 WL 176690 at *3. In summary, the Federal Circuit held that

> [m]ere improvement in properties does not always suffice to show unexpected results. In our view, however, when an applicant demonstrates *substantially* improved results, as Soni did here, and *states* that the results were *unexpected,* this should suffice to establish unexpected results *in the absence of* evidence to the contrary.

Soni, 54 F.3d at 751.

Here, there is an actual difference between the results obtained through the claimed invention and the prior art. As discussed above, the prior art teaches that 15-hydroxytestosterone is not pharmacologically active. Unexpectedly, the Applicants discovered that it is pharmacologically active. Thus, the first prong of the test is satisfied.

The second prong of the test is likewise satisfied. According to *Soni*, all that is required is a statement that the results were unexpected. The Applicants have provided such a statement in the specification. Specifically, the specification recites that "[t]he inventors have unexpectedly discovered that steroids which have not been used in therapeutic applications, i.e. 15-hydroxy or 16-hydroxy substituted testosterone analogues, meet the aforementioned requirements."[16] Just as the inventors in *Soni*, the Applicants have stated that the results were unexpected.

Since both prongs have been satisfied, the recited invention is patentable over the cited references because it is unexpected to discover that 15-hydroxytestosterones are pharmacologically active.

Point IV. It was unexpected to discover that 15-hydroxytestosterone is pharmacologically active when orally administered.

Moreover, it was unexpected to discover that 15-hydroxytestosterones are pharmacologically active when orally administered. As discussed above, one would have expected 15-hydroxytestosterone not to be pharmacologically active when orally administered. "Only a few androgens, e.g. dehydroepiandrosterone (DBEA) and 17α-alkylated derivatives of

[16] Specification at page 3, lines 3-5

testosterone, are suitable for oral administration because, unlike testosterone, they are largely resistant to hepatic metabolism. However, disadvantages of oral administration are associated with the bad absorption of these androgens and the relatively high effect they exert on the liver and particular the liver metabolism [*citation omitted*]. This is why, in existing protocols, androgens are generally administered in the form of 2-3 weekly depot injections or implants."[17]

Thus, there is an actual difference between the expected results and the results the Applicants discovered. The expected result was that 15-hydroxytestosterone would not be pharmacologically active when orally administered. However, Applicants actually discovered that 15-hydroxytestosterone is pharmacologically active when orally administered.

> Surprisingly, it was found that the hydroxytestosterone analogues according to the present invention combine adequate androgenic potency with acceptable oral bioavailability and minimum impact on liver metabolism. Consequently, the present androgens are particularly suited for any therapeutic applications for which androgens have been employed or recommended. The present hydroxytestosterone analogues may also be delivered effectively, particularly in relatively low dosages such as those typically required by females, by transmucosal or transdermal administration.[18]

This point is further supported by the specification at example 2.[19] Example 2 discusses an experiment to determine the *in vivo* androgenic potency of 15-substituted testosterone derivatives.[20] The results of the experiment establish that, contrary to the expectations based on what was known about 15-substituted testosterone derivatives, they were found to be "considerably more potent than the *in vivo* androgenicity observed after oral administration of DHT, a classical androgen and the active metabolite of testosterone *in vivo*."[21]

Thus, Applicants have satisfied the two-prong unexpected results tests. Just as in *Soni*, the Applicants have demonstrated an actual difference, and stated that the difference was unexpected.

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[17] Specification at page 2, lines 7-13.
[18] Specification at page 3, lines 6-12.
[19] Specification at page 11, line 14 to page 12, line 20.
[20] Specification at page 11, lines 16-21.
[21] Specification at page 12, lines 9-15.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and withdrawal of the asserted rejections, and allowance of pending claims 17, 20, 21, 23, 25-28 and 30. Should the Examiner like to discuss this application further, the Examiner is invited to contact the Applicants' undersigned representative at (412) 471-8815.

Respectfully submitted,

THE WEBB LAW FIRM

By: _____

William H. Logsdon
Registration No. 22,132
Attorney for Applicants
700 Koppers Building
436 Seventh Avenue
Pittsburgh, Pennsylvania 15219
Telephone: 412-471-8815
Facsimile: 412-471-4094
E-mail: webblaw@webblaw.com